As the collective nature of allosteric transitions make them well suited to be studied within the framework of ANM, we validate our findings on the αvβ3 integrin 1JV2 and its ligand bound form 1L5G using an all atom version of ANM. Using the formalism developed in this study, we show the intrinsic many-body nature of allosteric interactions and conformational changes triggered by them. We show how ligand binding perturbs the first 3 global vibrational modes by inducing collective responses up-to quaternary level and enhanced-many body correlations between the αv and β3 domains upon binding.

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2264-Pos Board B34

Exploring the Energy Landscapes of Protein Folding Simulations with Bayesian Computation

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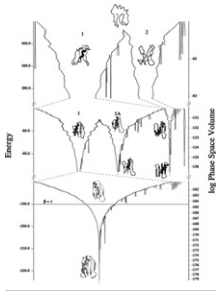
Nested sampling is a Bayesian sampling technique developed to explore probability distributions localised in an exponentially small area of the parameter space. The algorithm produces both posterior samples and an estimate of the evidence of the model. The nested sampling algorithm also provides an efficient way to calculate free energies and the expectation value of thermodynamic observables at any temperature, through a simple post-processing of the output. Previous applications of the algorithm have yielded large efficiency gains over other sampling techniques.

We describe a parallel implementation of the nested sampling algorithm and its application to the problem of protein folding in a Go-type force field of empirical potentials that were designed to stabilize secondary structure elements in room-temperature simulations. We demonstrate the method by conducting folding simulations on a number of small proteins which are commonly used for testing protein folding procedures. A topological analysis is performed to produce energy landscape charts, which give a high level description of the potential energy surface for the protein folding simulations. These charts provide qualitative insights into both the folding process and the nature of the model and force field used.



2265-Pos Board B35

NMR Characterization of the Structural Effects of Charge Repulsion in an Antibiotic Peptide Model

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Due to the decreasing effectiveness of common antibiotics, there is an overwhelming need for new antibiotics. One promising avenue is peptide antibiotics, which are generally helical and cationic. We are investigating peptide antibiotic models composed of the hydrophobic dialkylated amino acid Aib (α-aminoisobutyric acid), which imparts a strong 310-helical bias due to steric hindrance at the α-carbon. Cationicity is achieved by insertion of lysine residues. Previous studies have shown that insertion of adjacent neutral monoalkylated amino acids into an Aib sequence creates a region of reduced steric hindrance, allowing hydrogen-bonding solvents to disrupt the hydrogen bond that spans the insertion region, ultimately creating a kink in the helix. Separation of the monoalkylated residues by one turn leaves the helix undistorted. However, some studies suggest that insertion of charged residues one turn apart may distort helical structure. We report here the 3D NMR structural characterization of a model antibiotic peptide composed primarily of Aib, with two lysine residues placed one turn apart. Spectra were obtained in DMSO-d6 solution. Backbone and sidechain 1H and 13C resonances were assigned using natural abundance HSQC and CO-selective HMBC spectra. 1-D temperature dependence of amide chemical shifts indicated a 310-helical conformation with all intrahelical hydrogen bonds intact. Homonuclear ROESY crosspeaks were used to obtain 46 distance constraints, which together with the temperature data were used to calculate the structure using Xplor-NIH. The generated structure is fully 310-helical with a slight bend away from the charged face, likely due to charge repulsion. Thus, placement of charged amino acids has a small but noticeable effect on the structures of helical peptides even in a strongly hydrogen-bonding solvent. Our results indicate that the placement of cationic residues should be considered carefully in antibiotic peptide design.

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Structural Effects of Steric Hindrance Revealed by Sequence Permutation in Antibiotic Peptide Models

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Persistent infections caused by antibiotic-resistant microbes are a serious threat to public health. Peptide antibiotics, which tend to be helical, offer one promising solution. Incorporation of the sterically hindered amino acid Aib (α-aminoisobutyric acid) into designed peptide antibiotics has been shown to enhance helicity, increase protease resistance and maintain or even enhance bioactivity. Aib is known to impart a strong helical bias due to steric hindrance. However, the placement of less hindered monoalkylated amino acids in a predominantly Aib sequence can significantly perturb helical structure. We report here the 3D NMR structural characterization of two model antibiotic peptides composed primarily of Aib, with two alanine residues placed either one turn apart (AA36) or sequentially (AA45). Spectra were obtained in DMSO-d6 solution. Backbone and sidechain 1H and 13C resonances were assigned using natural abundance HSQC and CO-selective HMBC spectra. 1-D temperature dependence of amide chemical shifts in AA36 indicate a 310-helical conformation with all intrahelical H-bonds intact. However, in AA45, the H-bond to Aib6 is broken. Homonuclear ROESY crosspeaks were used to obtain distance constraints (46 for AA36, 69 for AA45), which together with the temperature data were used to calculate the structures using Xplor-NIH. The generated structure of AA36 is consistent with a canonical 310-helix. However, the structure of AA45 reveals a kink in the helix towards the two less sterically hindered Ala residues, breaking the H-bond to Aib6 (which spans the Ala residues). Amide H/D exchange kinetics on AA45 in CD3OD result in a pattern of exchange rate constants that is consistent with the variation in calculated H-bond lengths. Thus, placement of monoalkylated residues in an Aib sequence can have profound effects on helical structure and should receive due consideration in peptide antibiotic design.

2267-Pos Board B37

Characterizing Transition Pathways in the Transport Cycle of ABC Transporter MsbA

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MsbA is a member of the ABC (ATP-binding cassette) family transporters that uses energy from ATP hydrolysis to transport various substrates across cellular membrane. The transport cycle of MsbA has been described by a simple ''Alternating Access'' mechanism in which the transporter changes its conformation between an outward-facing (OF) and an inward-facing (IF) state while coupling the translocation of substrates. Here, to investigate the detailed transport cycle of MsbA at atomistic resolution, we have performed molecular dynamics (MD) simulations using a combination of several computational methods. Starting from the recently solved X-ray crystal structure of MsbA in OF state, we first generate high resolution all-atom models for the two IF states (IF open and IF closed) by using targeted MD simulations. We then define two collective variables to describe the relative motion of the two transmembrane domains (TMDs) and nucleotide binding domains (NBDs), respectively. Steered MD simulations along the collective variables have been performed to induce the conformational changes between the three states (OF, IF open and IF closed) of MsbA. Assessing the energetics associated with the induced transitions, approximated by calculating the non-equilibrium work involved in going from one state to another suggest that the OF-to-IF conformational transition follows two steps: the two TMDs close first, and then the two NBDs open, as opposed to the pathway observed from initial targeted MD simulations. Taken together, these results not only provide a better understanding of the functionality of ABC transporters, but also help define a general mechanism for membrane transport process.

2268-Pos Board B38

Conformational Analysis Reveals Distinct Mechanical Transduction Mechanisms of RecA-Like Molecular Motors

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A majority of ATP-dependent molecular motors are RecA-like proteins, performing diverse functions in biology. These RecA-like molecular motors consist of a highly conserved core containing the ATP-binding site. Here I examined how ATP binding within this core is coupled to the conformational changes of different RecA-like molecular motors. This study showed that dense hydrogen bond networks are prevalent in the ATP binding sites of RecA-like molecular motors when ATP is present, but the conformations of different RecA-like motors in the apo state are varying. Conserved hydrogen bond networks and conformational changes revealed two major mechanical